Personalizing Psychiatric Treatment Today

Rajiv Tandon, M.D.
Chief, Psychiatry Service, NF/SG VHA
Professor of Psychiatry,
University of Florida
Gainesville, Florida
Disclosure Information

NO CURRENT FINANCIAL CONFLICTS OF INTEREST

A CLINICIAN, CLINICAL RESEARCHER, & ADMINISTRATOR
Outline

An Introduction to Personalized Medicine

Personalized Psychiatry

Personalized Psychiatry & Recovery

Personalizing Treatment - The Model and the Future

Personalizing Treatment Today: Guidance for Best Practice
  - Measurement-based Care, Individualizing Services
Method

Review of the Literature

Consultation with Experts

- Charles Nemeroff
- Florian Holsboer
- James Kennedy
- Anil Malhotra
- Helen Mayberg

Clinical Experience

- Personal and Colleagues
Personalized medicine?

- Medicine has always been personalized.
- Personalized medicine and Patient Recovery are the same thing.
- Medicine will never be personalized.
- It is a change in expectation as well as some practical, process changes.
Outline

An Introduction to Personalized Medicine

Personalized Psychiatry and Recovery

Personalizing Treatment - The Model and the Future

Personalizing Psychiatric Treatment Today
  - A Case Example - Guidance for Best Practice
  - Measurement-based Care
  - Individualizing Services
The Problem in Medicine

• Multiple active regimens for the treatment of most diseases
• Variation in response to therapy
• Unpredictable toxicity

With choice comes decision
Pharmacogenomics – Under the Personalized Medicine Umbrella

<table>
<thead>
<tr>
<th>Better medication choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>– 100,000 Americans die annually and</td>
</tr>
<tr>
<td>2,000,000+ are hospitalized due to adverse reactions to medications</td>
</tr>
<tr>
<td>– Predict individual reactions to drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safer dosing options</th>
</tr>
</thead>
<tbody>
<tr>
<td>– More exact dosing, optimum result/side effect balance</td>
</tr>
</tbody>
</table>
“A surgeon who uses the wrong side of the scalpel cuts her own fingers and not the patient;

if the same applied to drugs they would have been investigated very carefully a long time ago”

Rudolph Buchheim

Beitrage zur Arzneimittellehre, 1849
Effectiveness of drugs:

- **Hypertension Drugs 10-30%**
  - ACE Inhibitors

- **Heart Failure Drugs 15-25%**
  - Beta Blockers

- **Anti Depressants 20-50%**

- **Cholesterol Drugs 30-70%**
  - Statins

- **Asthma Drugs 40-70%**
  - Beta-2-agonists
Personalized medicine takes into account individual genetic differences

- Traditionally, doctors used:
  - Family history
  - Socioeconomic circumstances
  - Environmental factors ++++

- Now:
  - genomic/genetic testing
  - proteomic profiling
  - metabolomic analysis (study metabolites)
Treatment of Any Disease Condition

• Know the Person with the Condition
  
  Know the Disease that you are treating

  Know the Treatments at your disposal

  Principles of Treatment

DEVELOP EVIDENCE-BASED GUIDELINES
We wouldn’t think of buying shoes in a single size

So why should we be satisfied with one-size-fits-all medicine?
“Personalized medicine is the use of diagnostic and screening methods to better manage the individual patient’s disease or predisposition toward a disease….

“Personalized medicine will enable risk assessment, diagnosis, prevention, and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health.”
Shift to Personalized Care
What Personal Information- A New Biomarker Toolbox

Human Genome Sequence (Genomics)  Polymorphisms ~ 10,000,000
Gene Expression Profiles (Transcriptomics)  RNA Microarrays of ~ 25,000 gene readouts or transcripts
Proteome (Proteomics)  Protein arrays of specific protein products ~ 100,000
Metabolome (Metabolomics)  Small molecule metabolites ~ 5000
The Path to Personalized Medicine

Standard of Care (A or B) → Random Selection A or B → Outcome

“Omics”-guided A or B → Outcome

Health and Economic Outcomes
Personalized Medicine: Definition

- **Personalized medicine** is the use of information from a patient's genotype to:
  - initiate a preventative measure against the development of a disease or condition,
  - select the most appropriate therapy for a disease or condition

  that is particularly suited to that patient.

Variations in our DNA make us UNIQUE!
Virtually All Diseases (Except Maybe Trauma) Have a Genetic Component

- Schizophrenia
- Major Depression
- PTSD

Genetic Component

Environmental Component
A SMALL SAMPLING OF COOL THINGS ABOUT THE GENOME

• Humans have fewer protein-coding genes than expected – only about 20,000
• Only about 1.5% of the human genome is involved in coding for protein, but there are numerous complex critical functions encoded in the rest of the DNA instruction book
• We are all 99.9% the same at the DNA level
Disease with Genetic Component

- Identify Genetic Defect(s)
  - Diagnostics
  - Pharmacogenomics
  - Preventive Medicine

Accelerated by Human Genome Project and HapMap

Therapeutic Developments
Pharmacogenetics

- Study of genetic variation that gives rise to different responses to drugs
- It is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects.
- Nongenetic factors include: age, organ function, concomitant therapy, drug interactions, and the nature of the disease.
Breast Cancer

1990

- Surgery
- Radiation
- Chemotherapy (drugs)

2012

- Surgery
- Radiation
- Chemotherapy
  - Specialized treatments (for certain types of breast cancer)

Why does Tumoricide work on some patients but not on others?
No Effect/Hurt | Helped

Why?
Two Types of Breast Cancer

- Tumoricide is a personalized medication
- Tumoricide *only* works for **Her2+** breast tumors
Personalized Psychiatry
A future dream ??
Old Paradigm:

Reactive Medical Care

- Diagnosis
- Select Drug
- Switch Drug
- Switch Drug Again

Disease Severity vs. Time
New Paradigm:

Efficient Medical Care

Disease Severity

"Right" Drug  Monitoring

Diagnosis/Prognosis

Predisposition  Screening

Time
Future Paradigm:

Preventive Medical Care

- Predisposition
- Screening
- Preventive Measures
- Monitoring

Disease Severity vs. Time
Case study: Nortriptyline metabolism

Three women of the same height, weight, age, and racial background are depressed and go to the doctor.

The doctor prescribes an antidepressant, Nortriptyline, at a dose of 100 mg.

- Person A has an adverse reaction
- Person B nothing happens
- Person C gets better…

Why?
ADME of Nortriptyline

100mg Nortriptyline

- A: Adverse reaction
- B: Nothing happens
- C: Gets better

95mg 5mg 50mg
DNA variation influence drug metabolism

Ultrarapid Metabolizer
5mg

Drug → Enzymes → Metabolites

check
http://www.2dsolutions.it/flash/gallery_med.htm
2012 - What do doctors do?

- **A** Poor Metabolizer: Decrease Dose
- **B** Ultrarapid Metabolizer: Increase Dose
- **C** Normal Metabolizer: Continue current dose

Or change drug
Personalized medicine remains a research concept – it is not yet ready for clinical practice!
Optimizing Individual Treatment Outcomes

Treatment and other services

Treatment (reduce symptoms and prevent relapse)
- Medications
- Cognitive behavioral therapy

Rehabilitation (enhance adaptive skills)
- Social skills training

Supports (environmental changes)
- Supported housing
- Supported employment

Costs and unintended adverse consequences
- Side effects
- Related health risks
- Fiscal costs
- Discrimination

Reduce disease burden

Add treatment burden

RECOVERY

Health and wellness
• Vocational and/or educational function
• Empowerment
• Physical health
• Instrumental competence
• Social integration
• Interpersonal fulfilment
• Quality of life
• Life Satisfaction
• Optimism/Hope

Pharmacological Treatment of Any Disease Condition

• **Know the Disease that you are treating**
  – Nature; Treatment targets; Treatment goals;

• **Know the Treatments at your disposal**
  – What they do; How they compare; Costs;

• **Principles of Treatment**
  – Measurement-based; Targeted; Individualized
DIMENSIONS OF SCHIZOPHRENIA

Negative symptoms

Positive symptoms

Motor symptoms

Mood symptoms

Cognitive deficits

Disorganization

Different underlying Pathophysiology and treatment response
Natural Course of Schizophrenia

AGE 10 15 17 20 25

Premorbid stage
Prodromal phase
Active phase
Remission phase
Residual phase

First treatment
Disease onset
Undetected/untreated illness
A Remitting and Relapsing Illness
Importance of Relapse Prevention

• Each relapse associated with (Short-Term)
  – Increased distress and dysfunction
  – Vocational and social disruption
  – Increased risk of suicide and violence
  – Increased costs of care

• With each relapse (LONG-TERM)
  – Subsequent recovery is less complete
  – Remission takes longer to achieve
  – Illness becomes more resistant to treatment
  – Regaining prior function level more difficult
Pharmacological Treatment of Schizophrenia

- Antipsychotics are the Mainstay
  - Variably effective on different treatment targets
  - Treatment of acute exacerbation
  - Prevention of psychotic relapse
**Options for Antipsychotic Therapies**

<table>
<thead>
<tr>
<th>Prior to Antipsychotics</th>
<th>Conventional or Typical Antipsychotics (First Generation)</th>
<th>Atypical Antipsychotics (Second Generation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1952: Chlorpromazine</td>
<td>1990s: Aripiprazole, Paliperidone, Iloperidone</td>
</tr>
<tr>
<td></td>
<td>1980s: Clozapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1990s: Risperidone, Olanzapine, Quetiapine, Ziprasidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000s:</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Selection with Antipsychotics

- All antipsychotics are effective against psychotic symptoms (positive/disorg.)
  - Clozapine more effective than other agents for refractory positive symptoms
- Each medication has:
  - unique side effects
  - unique pharmacokinetics
  - Different degrees of ease of use
- Individual patients may respond preferentially to different medications
With Antipsychotics, Objective is Maximal Antipsychotic Effect without EPS +

- Fewer EPS
- Fewer negative symptoms
- Less tardive dyskinesia
- Better cognition
- Less noncompliance
- Less depression

Greater Ease of Obtaining Antipsychotic Effect Without EPS

EPS=acute extrapyramidal symptoms.
Minimizing Side-Effects of Antipsychotic Treatment

All Side-effects involve interactions between

(i) individual patient vulnerability,
(ii) specific agent profile, and
(iii) how the agent is utilized

- EPS
- Metabolic side-effects
- Other side-effects
Steps in Antipsychotic Therapy
Dosing, Duration, Sequence

• Proper antipsychotic trial sequence:
  – Start with a systematic 6-10 week trial of one antipsychotic with optimal dosing.
  – If needed, follow with systematic monotherapy with another agent at adequate dose and duration.
  – If needed, follow with a trial of clozapine or a long-acting agent.
  – Follow with a trial of clozapine, if not tried before.

• Only then should other strategies be considered.
  – e.g., antipsychotic polypharmacy.
Guidelines for Good Practice
Measurement-based, Individualized

• Ongoing, careful monitoring is critical!
  – Reliable and repeated assessment of the efficacy of treatment using defined treatment targets.
    • Use of standard rating scales will facilitate this goal—BPRS, CGI.
  – Careful assessment of possible adverse effects of treatment.
    • Protocols for health monitoring
  – Ongoing collaboration with patient in decision-making.

• Standard protocols should be customized in response to individual vulnerabilities/needs and specific agent.
Pharmacological Treatment of Any Disease

• Know the Disease that you are treating
  – Nature; Treatment targets; Treatment goals;

• Know the Treatments at your disposal
  – What they do; How they compare; Costs;

• Principles of Treatment
  – Measurement-based; Targeted; Individualized
DIMENSIONS OF SCHIZOPHRENIA

Different underlying Pathophysiology and treatment response

- Positive symptoms
- Negative symptoms
- Motor symptoms
- Mood symptoms
- Cognitive deficits
- Disorganization
## Diagnosis-Specific Severity Assessment: Symptom Domains

<table>
<thead>
<tr>
<th>Symptom Domain</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>0 = Not Present</td>
</tr>
<tr>
<td>Delusions</td>
<td>1 = Equivocal</td>
</tr>
<tr>
<td>Disorganized Speech</td>
<td>2 = Present, but mild</td>
</tr>
<tr>
<td>Abnormal Psychomotor Behavior (catatonia)</td>
<td>3 = Present &amp; moderate</td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td>4 = Present &amp; severe</td>
</tr>
<tr>
<td>Impaired Cognition</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Application
Dimensions of Psychotic Disorders

• Precision in measurement-based care

• Specific targeting of distinct dimensions of schizophrenia and other psychotic disorders

• Individualizing treatment with more precise response-based treatment adjustments

• FOUR CLINICAL VIGNETTES

Guidelines for Pharmacological Treatment of Schizophrenia

LEVEL 0. COMPREHENSIVE ASSESSMENT

LEVEL 1. Monotherapy with an antipsychotic (SGA or FGA) other than clozapine

LEVEL 2. If Level 1 ineffective or not tolerated: FGA or different SGA

LEVEL 3. If Level 1 and 2 ineffective or not tolerated:
Clozapine or long-acting antipsychotic agent

LEVEL 4. If Levels 1-3 ineffective or not tolerated:
   Clozapine if not tried earlier
   SGA or FGA + ECT
   Clozapine augmentation with SGA or FGA, if clozapine monotherapy not successful
   SGA or FGA augmentation with anticonvulsant
   Other antipsychotic combinations (if partial response with one agent)
Optimizing Individual Treatment Outcomes

**Treatment and other services**

- **Treatment** (reduce symptoms and prevent relapse)
  - Medications
  - Cognitive behavioral therapy
- **Rehabilitation** (enhance adaptive skills)
  - Social skills training
- **Supports** (environmental changes)
  - Supported housing
  - Supported employment

**Costs and unintended adverse consequences**
- Side effects
- Related health risks
- Fiscal costs
- Discrimination

**Reduce disease burden**

**Add treatment burden**

**RECOVERY**

- Health and wellness
  - Vocational and/or educational functioning
  - Independent living
  - Physical health
  - Instrumental competence
  - Social integration
  - Quality of life

THANK YOU!

Discussion